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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/714,409	11/14/2000	Leisa Johnson	ONYX1033ord	5051

7590 12/22/2003

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EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/714,409	JOHNSON ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on 17 September 2003.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,4,5,7,8,11,12 and 14 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 1,4,5,7,8,11,12 and 14 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claims 1, 4, 57, 8, 11, 12, 14 have been amended, claims 2-3, 6, 9-10, 13, 15 and 16 have been canceled by the amendment filed September 17, 2003.

Claims 1, 4, 5, 7, 8, 11, 12, 14, to which the following grounds of rejection are applicable, are pending.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 4, the "said viral vector" is vague since the base claim does not recite "a viral vector" *per se* but rather "An adenoviral vector". A change to – wherein said adenoviral vector – is suggested.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 5, 7, 8, 11, 12, 14, are rejected under 35 USC 103(a) as being unpatentable over McCormick I (US Pat No. 5,666,178) or McComick II (US Pat No. 5,801,029) taken with Yu or Fines.

Both McCormick I and II teach a cancer therapeutic composition comprising an adenovirus comprising a mutation in the E1a region so as to cause a loss of RB binding to the protein encoded by the E1a region (entire disclosures). The concept as taught in the cited McCormick I and II is that the administered adenovirus is able to target preferentially neoplastic cells lacking p53 or RB function.

Both McCormick I and II do not teach the use of a E2F responsive promoter in the adenovirus in order to control the expression of an early adenoviral gene, wherein the promoter is positioned at the deletin site of an endogenous adenoviral E1a promoter.

However, Yu teaches the same throughout the reference, specifically pages 7, 9 and 13 and the claims.

More specifically, pages 7, 11, and 13, respectively, state:

> **[0088]** Accordingly, in one embodiment, the invention provides an adenoviral vector in which an adenoviral gene (preferably a gene necessary for replication) is under transcriptional control of a cell status-specific TRE, wherein the cell status-specific TRE comprises a cell cycle-activated, or cell-cycle specific, TRE. In one embodiment, the cell cycle-activated TRE is an E2F1 TRE. In one embodiment, this TRE comprises the sequence depicted in FIG. 3 and SEQ ID NO:2.

> **[0105]** When a cell status-specific TRE is used with an adenovirus gene that is essential for propagation replication competence is preferentially achievable in the target cell expressing cell status. Preferably, the gene is an early gene, such as E1A, E1B, E2, or E4. (E3 is not essential for viral replication.) More preferably, the early gene under cell status-TRE control is E1A and/or E1B. More than one early gene can be placed under control of an cell status-specific TRE. Example 1 provides a more detailed description of such constructs.

> **[0139]** The adenoviral vectors may be delivered to the target cell in a variety of ways, including, but not limited to, liposomes, general transfection methods that are well known in the art (such as calcium phosphate precipitation or electroporation), direct injection, and intravenous infusion. The means of delivery will depend in large part on the particular adenoviral vector (including its form) as well as the type and location of the target cells (i.e., whether the cells are in vitro or in vivo).

Fine teaches and discloses the advantages of using an E2F responsive promoter (page 9) as a tumor specific promoter so as to improve the killing of tumor cells using any cancer gene therapy vector available in the prior art of record (pages 3 and 4). More specifically, Fine teaches that a vector such as an adenoviral vector (page 12 bridging page 13) can be used to carry an E2F responsive promoter operably linked to a heterologous gene of interest, preferably encoding a negative potentiator (page 4), and that the use of such vectors result in high selectivity *in vivo* between malignant and non-malignant cells (page 4).

One of ordinary skill in the art would have been motivated to further incorporate

the E2F responsive promoter according to the teaching of Yu in the adenovirus vector of both McCormick(s). One of ordinary skill in the art would have been motivated to do so because such use of the E2F responsive promoter instead of the endogenous adenoviral E1a promoter would further ensure that the adenovirus vectors of McCormick(s) would only replicate in proliferating cells such as tumors cell lacking p53 or Rb function, wherein this teaching of the motivation is found in both Yu and Fine referenes.

Thus, the claimed invention as a whole, was *prima facie* obvious.

Claims 1, 4, 5, 7, 8, 11, 12, 14, are ejected under 35 U.S.C. 103(a) as being unpatenble over either Hallenbeck (US Pat No. 5,998,205) or Gregory (US 2003/0026789), taken with Fine (WO 98/13508), and further in view of McCormick I (US Pat No. 5,666,178) or McComick II (US Pat No. 5,801,029)

Both Hallenbeck (columns 4, 6, 10-14, particularly columns 13, and 27-28) and Gregory (pages 4, 5 and 7) teaches a replication-competent adenovirus vectors comprising a tumor specific transcription regulatory sequence operably linked to at least one replication gene of the adenoviral vector, and the use of the vectors to kill cancer cells by contacting the cancer cells with the adenovirus vectors. Both references teach that tissue specific or cell specific regulatory sequences such as promoters and enhancers are operably linked to virus genes essential for replication functions, and that these genetic sequences are specifically activated or derepressed in the target tissue,

and the invention are essential directed to cancer gene therapy methods for tissue-specific replication using these vectors in target cancer cells.

Hallenbeck and Gregory do not teach that the tissue or cell specific promoter is an E2F responsive promoter. However, at the time the invention was made, Fine teaches and discloses the advantages of using an E2F responsive promoter (page 9) as a tumor specific promoter so as to improve the killing of tumor cells using any cancer gene therapy vector available in the prior art of record (pages 3 and 4). More specifically, Fine teaches that a vector such as an adenoviral vector (page 12 bridging page 13) can be used to carry an E2F responsive promoter operably linked to a heterologous gene of interest, preferably encoding a negative potentiator (page 4), and that the use of such vectors result in high selectivity *in vivo* between malignant and non-malignant cells (page 4).

It would have been obvious for one of ordinary skill in the art to employ an E2F responsive promoter (page 9 of Fine) as the cancer cell specific promoter in the adenoviral vector system of either Hallenbeck or Gregory. One of ordinary skill in the art would have been motivate to employ the E2F responsive promoter as the cancer cell specific promoter in the adenoviral vector system of either Hallenbeck or Gregory because Fine teaches and discloses the advantages of using an E2F responsive promoter as a tumor specific promoter so as to improve the killing of tumor cells using any cancer gene therapy vector available in the prior art of record, and because both Hallenbeck and Gregory teaches that if a target tissue is cancer cells containing target tissue, any promoter specific to the tissue or cancer cells of the tissue can be used in an

adenoviral vector so as to control the expression of an adenovirus early gene in the tissue, wherein expression of the early gene as the result of the induced activity of the promoter would result in the killing of the cancer cells in the target tissue.

With respect to the teaching of the newly amended limitation which specifically recites a mutation in the E1a region of the administered adenoviral vector,

Both McCormick I and II teach a cancer therapeutic composition comprising an adenovirus comprising a mutation in the E1a region so as to cause a loss of RB binding to the protein encoded by the E1a region (entire disclosures). The concept as taught in the cited McCormick I and II is that the administered adenovirus is able to target preferentially neoplastic cells lacking p53 or RB function.

As such, it would have been also obvious for one of ordinary skill in the art to incorporate a mutation in the E1a region so as to cause a loss of RB binding to the protein encoded by the E1a region. One of ordinary skill in the art would have been motivated to do so because both McCormick I and II teach and suggest that by employing the mutation in the E1a region of an administered anti-tumor adenovirus, the administered adenovirus is able to target preferentially neoplastic cells lacking p53 or RB function, and such incorporation of the mutation would further ensure that only tumor cells including those that lack p53 or Rb function are targeted for killing and replication by the administered adenovirus.

Thus, the claimed invention as a whole was *prima facie* obvious.

Applicant's latest response has been considered by the examiner but is not found persuasive in view of the new grounds of the rejection.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Please note that the examiner is expected to move to a new US PTO office building located in Alexandria on January 12, 2004. The examiner office phone number at the new building is **571-272-0731.**

DAVE T. NGUYEN
PRIMARY EXAMINER